

Clinical course and treatment efficacy of COVID-19 near Hubei Province, China: A multicentre, retrospective study

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Abstract

Currently, COVID-19 has been reported in nearly all countries globally. To date, little is known about the viral shedding duration, clinical course and treatment efficacy of COVID-19 near Hubei Province, China. This multicentre, retrospective study was performed in 12 hospitals in Henan and Shaanxi Provinces from 20 January to 8 February 2020. Clinical outcomes were followed up until 26 March 2020. The viral shedding duration, full clinical course and treatment efficacy were analysed in different subgroups of patients. A total of 149 COVID-19 patients were enrolled. The median age was 42 years, and 61.1% (91) were males. Of them, 133 (89.3%) had fever, 131 of 144 (91%) had pneumonia, 27 (18.1%) required intensive care unit (ICU) management, 3 (2%) were pregnant, and 3 (2%) died. Two premature newborns were negative for SARS-CoV-2. In total, the median SARS-CoV-2 shedding period and clinical course

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were 12 (IQR: 9–17; mean: 13.4, 95% CI: 12.5, 14.2) and 20 (IQR: 16–24; mean: 21.2, 95% CI: 20.1, 22.3) days, respectively, and ICU patients had longer median viral shedding periods (21 [17–24] versus 11 [9–15]) and clinical courses (30 [22–33] vs. 19 [15.8–22]) than non-ICU patients (both $p < .0001$). SARS-CoV-2 clearances occurred at least 2 days before fatality in 3 non-survivors. Current treatment with any anti-viral agent or combination did not present the benefit of shortening viral shedding period and clinical course (all $p > .05$) in real-life settings. In conclusion, the viral shedding duration and clinical course in Henan and Shaanxi Provinces were shorter than those in Hubei Province, and current anti-viral therapies were ineffective for shortening viral shedding duration and clinical course in real-world settings. These findings expand our knowledge of the SARS-CoV-2 infection and may be helpful for management of the epidemic outbreak of COVID-19 worldwide. Further studies concerning effective anti-viral agents and vaccines are urgently needed.

KEYWORDS

anti-viral efficacy, clinical course, Coronavirus disease 2019 (COVID-19), epidemiology, Henan Province, Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), Shaanxi Province

1 | INTRODUCTION

In December 2019, a novel coronavirus infection was first reported in Wuhan of Hubei Province, China, and then, a public health emergency of international concern was declared by the World Health Organization (WHO) (Li et al., 2020; Wang, Horby, Hayden, & Gao, 2020; Wang & Zhang, 2020; Zhu et al., 2020). Recently, the 2019 novel coronavirus was named 'severe acute respiratory syndrome coronavirus 2' (SARS-CoV-2) by the International Committee on Taxonomy of Viruses (ICTV, 2020). SARS-CoV-2 is a positive-sense single-stranded RNA virus belonging to the genus *Betacoronavirus*. It is an enveloped, round or oval-shaped particle, and the polymorphism of the virus is commonly observed and has been assigned to an existing species of hundreds of known viruses largely isolated from bats (Decaro & Lorusso, 2020). Currently, SARS-CoV-2-associated disease has been named 'coronavirus disease 2019 (COVID-19)' by the WHO (WHO, 2020c), and it has been reported in almost all countries worldwide and characterized as a pandemic by the WHO (WHO, 2020b). Unfortunately, no effective drugs are clinically approved by the authorities globally because of the absence of evidence (Holshue et al., 2020; Kim et al., 2020).

It is known that some COVID-19 patients have developed severe pneumonia, acute respiratory distress syndrome (ARDS), shock or multiple organ failure (Chen et al., 2020; Huang et al., 2020; Wang, Hu, et al., 2020). Of them, 23%–32% required admission to the intensive care unit (ICU) and 4.3%–15% died (Chen et al., 2020; Huang et al., 2020; Wang, Hu, et al., 2020). Recently, several studies have described the epidemiological and clinical characteristics of patients from Wuhan City (Chen et al., 2020; Huang et al., 2020; Wang, Hu, et al., 2020) or far away from Hubei Province (Chang et al., 2020; Xu et al., 2020). To date, there is no large-scale research to mainly focus

on the viral shedding duration, clinical course and treatment efficacy of COVID-19 patients near Hubei Province, especially Henan Province, which had the third and second largest numbers of total COVID-19 patients and fatalities as of 23 March 2020 in China, respectively (WHO, 2020a). Since the patients near Hubei Province may represent second- and third-generation (wave) of infections, understanding these conditions of COVID-19 near Hubei Province may have important implications that will help to control further spread of the disease in China and worldwide.

2 | METHODS

2.1 | Data sources

This retrospective, multicentre, observational study includes COVID-19 patients from 12 centres in Henan and Shaanxi Provinces, China. According to the arrangements put in place by the local government, all suspected COVID-19 patients were admitted centrally to the designated local hospitals. Therefore, we retrospectively collected and analysed the epidemiological, clinical, laboratory, virological, management and outcome data of patients with laboratory-confirmed SARS-CoV-2 infection.

2.2 | Definition of laboratory-confirmed COVID-19

Throat swab specimens from the upper respiratory tract were obtained from all suspected patients during their first visits to the hospital. Laboratory-confirmed COVID-19 was diagnosed according to WHO interim guidance (WHO, 2020d). Laboratory

confirmation of SARS-CoV-2 infection was performed in nine different Centers for Disease Control and Prevention (CDCs) of government, the CDCs of Henan and Shaanxi Provinces, the CDCs of Xinyang, Nanyang, Anyang, Shangqiu, Luoyang and Hebi cities of Henan Province, and the CDC of Yan'an City of Shaanxi Province. The diagnostic reagents of RT-PCR were provided by the four companies (Shanghai Huirui Biotechnology, Shanghai BioGerm Medical Biotechnology, Shanghai GeneoDx Biotechnology and Shanghai Zhijiang Biotechnology).

2.3 | The principle and protocol of detection for SARS-CoV-2

The aforementioned kits were all designed for the qualitative detection of SARS-CoV-2, and the results indicate the presence of SARS-CoV-2 RNA and can be used to support the diagnosis of SARS-CoV-2 infection. The SARS-CoV-2 specific primers and TaqMan probes in the reaction system are designed targeting the ORF1ab and N genes conserved in virus genome. After nucleic acid extraction from clinical specimens, one-step RT-PCR amplification is performed, and the fluorescence signal is detected; a real-time amplification curve is produced by the software system automatically. A set of human housekeeping gene-specific primers and the corresponding probe are also included in the detection system as internal control, to avoid false negative caused by unqualified specimen collection, poor nucleic acid recover or failure of PCR.

Taking the kit of Shanghai BioGerm Medical Biotechnology as an example, the detailed protocols of RT-PCR were described as follows. This kit is compatible with multi-channel fluorescence PCR instruments, such as ABI 7500 real-time PCR instrument. 1. Reagent preparation (in reagent preparation area). Thaw the RT-PCR Reaction Mix r, RT-PCR Enzyme Mix and SARS-CoV-2 reaction mix at room temperature and spin briefly after mixing on a vortex mixer. Calculate the number of reactions (N) ($N = \text{number of specimens} + 1 \text{ positive control} + 1 \text{ negative control} + 1$) and prepare the master mix according to the following table by adding to an appropriate volume of centrifuge tube. Spin the tube briefly after mixing completely and add 20 μl of master mix to required wells of plate or PCR tubes in PCR Clean Room. 2. Specimen processing (in specimen processing area). (a) Nucleic acid extraction: the specimens to be tested, positive control and negative control are processed according to the instructions of the nucleic acid extraction kit. (b) Adding specimens: add 5 μl each of the nucleic acid of the specimens to be tested, positive control and negative control to the prepared PCR plates or tubes, and the final volume is 25 μl /reaction. Cap the tubes or the plates securely and centrifuge tubes or plates to collect the liquid in the bottom immediately. (c) PCR amplification (in PCR amplification area). (a) Place the PCR reaction tubes/plates in a fluorescent quantitative PCR instrument for amplification. (b) Cycling conditions: step 1 of reverse transcription (50°C, 10 min, 1 cycle), step 2 of pre-denaturation

(95°C, 5 min, 1 cycle), step 3 of denaturation (95°C, 10 s, 40 cycles) and annealing/elongation/fluorescence detection (55°C, 40 s, 40 cycles). 4. Parameter setting for result analysis. Baseline setting: adjust the start and end values according to the post-amplification melting-curve analysis (it is recommended to set the start value at 3–15 and end value at 5–20. At the same time, adjust the negative control's amplification curve to be straight or below the baseline.), and click 'Analysis' to obtain the analysis result automatically and review the results at the Report Interface. The test values of ORF1ab and N of the clinical specimens are determined using the ROC curve method with a cycle threshold of 38. Additionally, the limit of detection was 1×10^3 copies/ml, the positive/negative reference compliance rate within the company was 100%, and no cross-reaction with the known pathogens and reaction is not interfered by addition of interference substances.

2.4 | Data collection

Data were extracted from the electronic medical records and recorded in a pre-designed case report form. We extracted epidemiological, demographic, clinical, laboratory, management and outcome data from the relatively complete electronic medical records of patients in 12 centres from 20 January to 8 February 2020. Clinical outcomes were followed up until 26 March 2020. If data were missing from the records or if clarification was needed, we obtained data by direct communication with attending doctors or other healthcare providers. All data were checked by three physicians.

2.5 | Study outcomes

The primary endpoints were SARS-CoV-2 shedding duration and full clinical course. The secondary endpoints were admission to the intensive care unit (ICU) and fatality. The SARS-CoV-2 shedding period indicates the duration from the first SARS-CoV-2 RNA-positive result to the first SARS-CoV-2 RNA-negative result. The full clinical course indicates the duration from the onset of illness to the second SARS-CoV-2 RNA-negative result (the discharge time point for the majority of patients), discharge or fatality. The interval between the first and second SARS-CoV-2 RNA-negative results was at least 48 hr.

2.6 | Main criterion for hospital discharge

The criteria for hospital discharge (recovery) were the same as those described by Lan et al. (2020). Briefly, the criteria for hospital discharge were mainly based on the recovery of symptoms and signs, the clearance of SARS-CoV-2 RNA and the absorption of lung inflammations (such as ground-glass opacities and/or consolidations). SARS-CoV-2 RNA clearance should be confirmed at least two times with an interval of more than 48 hr.

2.7 | Statistical analysis

Continuous and categorical variables are presented as the median (interquartile range, IQR) and *n* (%), respectively. The Mann-Whitney U test, chi-squared test or Fisher's exact test were used to compare the differences between various subgroups where appropriate. Analyses were carried out using SPSS statistical software, version 16.0 (IBM). A *p* value of <.05 was set as the threshold for statistical significance.

3 | RESULTS

3.1 | Demographics and epidemiological and clinical characteristics at baseline

In total, 149 hospitalized COVID-19 patients were enrolled and analysed in this study. Of them, the median age of patients was 42 years (range 2–91), and 114 (76.5%) were 21–60 years old. There were 91 (61.1%) males and 3 pregnant women in this cohort. None of the patients had a history of exposure to the Huanan seafood wholesale market. Seventy-six (51%) patients had been to Hubei Province over the past two months before illness onset, and 35 (23.5%) had been exposed to laboratory-confirmed cases of COVID-19 despite not being to Hubei Province recently. Hypertension (24, 16.1%), chronic liver diseases (13, 8.7%), diabetes (11, 7.4%), cardiovascular diseases (8, 5.4%) and respiratory system diseases (5, 3.4%) were the most common comorbidities (Table 1).

Overall, fever (133, 89.3%) was the most common symptom, followed by cough (95, 63.7%), fatigue (53, 35.6%), shortness of breath (37, 24.8%), dyspnoea (23, 15.4%), anorexia (20, 13.4%) and myalgia (18, 12.1%). Other symptoms included rigour, runny nose, diarrhoea, pharyngalgia, headache, nausea, chest pain, dizziness, vomiting and haemoptysis (Table 1). Ninety-five (63.7%) patients had three or more above-mentioned signs or symptoms. Notably, 8 (5.4%) patients did not have any signs or symptoms, that is asymptomatic COVID-19 cases.

3.2 | Laboratory characteristics on admission

Of the 149 patients, leucocytes below the lower limit of the normal range were observed in 29 (19.5%) patients, and leucocytes above the upper limit of the normal range were recorded in 12 (8.1%) patients (Table 2). More than half of the patients (76/149) presented decreased lymphocytes to less than the lower limit of the normal range, and 12.9% (19/147), 15% (22/147) and 10.2% (15/147) of patients had elevated levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST) and gamma-glutamyltransferase (GGT), respectively. Approximately one-third of patients had abnormal myocardial zymograms, which were reflected by the elevations of lactate dehydrogenase (LDH) in 47 (32%) patients and the elevations of creatine kinase in 9 (6.1%) patients (Table 2). Most patients (79.2%) had serum C-reactive protein (CRP) and erythrocyte sedimentation rates (ESRs) (70.1%) greater than the upper limit of the normal range

TABLE 1 Demographics and baseline characteristics of COVID-19 patients

	COVID-19 patients (n = 149)
Age, years	
Median (range)	42 (30–55)
2–10	8 (5.4%)
11–20	6 (4%)
21–30	27 (18.1%)
31–40	33 (22.1%)
41–50	29 (19.5%)
51–60	25 (16.8%)
61–70	9 (6%)
71–80	10 (6.7%)
81–90	1 (0.7%)
91	1 (0.7%)
Sex	
Female	58 (38.9%)
Male	91 (61.1%)
Occupation	
Agricultural worker	39 (26.2%)
Employee	32 (21.4%)
Technical worker	20 (13.4%)
Retired	18 (12.1%)
Self-employed	11 (7.4%)
Student	11 (7.4%)
Professionals [†]	10 (6.7%)
Unemployed	4 (2.7%)
Child	4 (2.7%)
Huanan seafood wholesale market exposure	
No	149 (100%)
Been to Hubei province before illness onset	
Yes	76 (51%)
No	73 (49%)
Expose to COVID-19 family members or patients	35 (23.5%)
Pregnancy	3 (2%)
Current Smoking	4 (2.7%)
Current alcohol abuse	7 (4.7%)
Chronic comorbidity	
Hypertension	24 (16.1%)
Chronic liver diseases	13 (8.7%)
Diabetes	11 (7.4%)
Cardiovascular diseases	8 (5.4%)
Respiratory system diseases	5 (3.4%)
Cerebrovascular diseases	3 (2%)
Malignant tumour	3 (2%)
Moderate or severe anaemia	2 (1.3%)

(Continues)

TABLE 1 (Continued)

	COVID-19 patients (n = 149)
Thyroid disease	2 (1.3%)
Chronic kidney disease	1 (0.7%)
Signs and symptoms	
Fever	133 (89.3%)
Highest temperature, °C	
<37.3	16 (10.7%)
37.3–38	59 (39.6%)
38.1–39	61 (40.9%)
39.1–40	12 (8.1%)
>40	1 (0.7%)
Cough	95 (63.7%)
Dry cough	51 (34.2%)
Productive cough	44 (29.5%)
Fatigue	53 (35.6%)
Shortness of breath	37 (24.8%)
Dyspnoea	23 (15.4%)
Anorexia	20 (13.4%)
Myalgia	18 (12.1%)
Rigour	14 (9.4%)
Runny nose	12 (8.1%)
Diarrhoea	11 (7.4%)
Pharyngalgia	10 (6.7%)
Headache	10 (6.7%)
Nausea	8 (5.4%)
Chest pain	7 (4.7%)
Dizziness	5 (3.4%)
Vomiting	4 (2.7%)
Haemoptysis	2 (1.3%)
More than three above-mentioned signs or symptoms	95 (63.7%)
Respiratory rate >24 breaths per minute	36 (24%)
Days from illness onset to admission	5 (3–7)

Note: Data are presented as the median (IQR) or n (%).

Abbreviations: COVID-19, coronavirus diseases 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2. †Including two healthcare workers.

(Table 2). One (0.7%) patient had co-infection with *Mycoplasma pneumoniae*, and 10 (6.7%) patients had the evidence of co-infection with bacteria on admission.

3.3 | Radiological characteristics on admission

Of the 149 laboratory-confirmed cases, 13 (9%) of the 144 patients for whom chest CT scans were available patients did not have pneumonia manifestations on CT examinations on admission. Of the 131

TABLE 2 Laboratory and chest CT results of COVID-19 patients on admission

	COVID-19 patients (n = 149)
Blood routine	
Leucocytes ($\times 10^9/L$; normal range 3.5–9.5)	4.8 (3.8–6.2)
Increased	12 (8.1%)
Decreased	29 (19.5%)
Neutrophils ($\times 10^9/L$; normal range 1.8–6.3)	3.1 (2.2–4.5)
Increased	17 (11.4%)
Lymphocytes ($\times 10^9/L$; normal range 1.1–3.2)	1.1 (0.7–1.5)
Decreased	76 (51%)
Haemoglobin (g/L; normal range 130–175)	140 (126–154)
Decreased	48 (32.2%)
Platelets ($\times 10^9/L$; normal range 125–350)	182 (147–227.5)
Increased	1 (0.7%)
Decreased	20 (13.4%)
Blood biochemistry	
Alanine aminotransferase (U/L; normal range 0–40)	21 (15–31)
Increased	19/147 (12.9%)
Aspartate aminotransferase (U/L; normal range 0–40)	25 (20–35)
Increased	22/147 (15%)
Gamma-glutamyltransferase (U/L; normal range 0–58)	30 (20–45)
Increased	15/147 (10.2%)
Alkaline phosphatase (U/L; normal range 40–130)	60 (50–73)
Increased	8/147 (5.4%)
Albumin (g/L; normal range 35–55)	41.4 (38–45)
Decreased	24/147 (16.3%)
Total bilirubin ($\mu\text{mol/L}$; normal range 0–25)	10.1 (7.2–14)
Increased	2/147 (1.4%)
Creatine kinase ($\mu\text{mol/L}$; normal range 20–115)	79 (54–130)
Increased	9/147 (6.1%)
Lactate dehydrogenase (U/L; normal range 75–250)	209 (158–258)
Increased	47/147 (32%)
Glucose (mmol/L; normal range 3.9–6.1)	5.6 (5–6.8)
Increased	52/147 (35.4%)
Decreased	3/147 (2%)
Serum potassium (mmol/L, normal range 3.5–5.5)	4 (3.6–4.2)
Increased	1/147 (0.7%)
Decreased	10/147 (6.8%)
Serum sodium (mmol/L, normal range 135–153)	139.3 (137–142)

(Continues)

TABLE 2 (Continued)

	COVID-19 patients (n = 149)
Increased	0/147 (0)
Decreased	19/147 (12.9%)
Coagulation function*	
Prothrombin time (s; normal range 9–14)	11 (10.1–12.1)
Increased	1/147 (0.7%)
Decreased	4/147 (2.7%)
Prothrombin time activity percentage (%; normal range 70–140)	100 (88.6–112)
Decreased	4/147 (2.7%)
D-dimer (mg/L; normal range 0–0.55)	0.31 (0.21–0.60)
Increased	39/147 (26.5%)
Infection-related biomarkers	
C-reactive protein (mg/L; normal range 0–5)	15.8 (7.1–38.2)
Increased	118 (79.2%)
Erythrocyte sedimentation rate (mm/h; normal range 0–15)	26 (14–43.5) [†]
Increased	96/137 (70.1%)
Procalcitonin (ng/mL; normal range 0–0.046)	0.052 (0.023–0.106) ^{††}
Increased	78/143 (54.5%)
Existence of co-infection	
Bacteria	12 (8.1%)
Fungus	10 (6.7%)
Mycoplasma	1 (0.7%)
Chest CT findings	
Normal	13/144 (9%)
Unilateral pneumonia	24/144 (16.7%)
Bilateral pneumonia	107/144 (74.3%)
Multiple mottling and ground-glass opacity	104/144 (72.2%)
Pleural effusion	4/144 (2.8%)

Note: Data are presented as the median (IQR), *n* (%) or *n/N* (%), where *N* is the total number of patients with available data. Increased indicates over the upper limit of the normal range and decreased indicates below the lower limit of the normal range. Abbreviation: COVID-19, coronavirus diseases 2019.

(91%, 131/144) patients who had pneumonia imaging findings, 24 had unilateral pneumonia, 107 had bilateral pneumonia, 104 had multiple mottling and ground-glass opacity, and 4 patients had pleural effusion (Table 2). Additionally, typical dynamic changes in a patient's chest CT images from admission to SARS-CoV-2 RNA clearance are presented in Figure 1.

3.4 | Differences between ICU and non-ICU patients

Of the 149 patients, 27 (18%) were admitted to the ICU within one week after hospitalization (Table 3). Compared with the 122 non-ICU

patients, the 27 ICU patients had a higher proportion of patients aged more than 70 years ($p < .0001$); decreased lymphocyte count ($p = .002$); increased ESR, CRP and procalcitonin levels (all p values $< .0001$); and increased ALT and LDH levels on admission (both p values $< .0001$). Additionally, hyponatremia ($p < .0001$) and high serum D-dimer levels ($p = .005$) were more common in ICU patients than in non-ICU patients on admission. More ICU patients than non-ICU patients presented dyspnoea and respiratory rates of more than 24 breaths per minute on admission (both p values $< .0001$).

3.5 | Three pregnant women with COVID-19 and two premature newborns

Two of three pregnant women were in the third stage of pregnancy. Both of them experienced foetal heart rate instability and possible foetal respiratory distress and required early delivery by caesarean section at the 30th and 37th weeks of gestation, respectively. Fortunately, two (with an interval of 48 hr) SARS-CoV-2 RNA-negative results for throat swab samples were observed in both newborns. One pregnant patient developed ARDS, required invasive mechanical ventilation and ECMO treatment, and eventually died on day 33 after delivery. Her baby's chest CT showed pneumonia and was uneventful recovery followed by close monitoring and supportive treatment.

3.6 | Management of COVID-19 patients

For the management of the patients, 80 (58%) of 138 patients receiving treatment accepted anti-viral treatment, including oseltamivir (75 mg every 12 hr, orally), interferon α (2–3 times every 24 hr, aerosol inhalation), or lopinavir and ritonavir tablets (500 mg twice daily, orally) alone or in combination (Table 4). The duration of anti-viral treatment was 6–11 days (median 8 days [IQR 7–10]). Twenty-five (16.8%) and 26 (17.4%) patients received short-term (3–5 days) glucocorticoids and intravenous immunoglobulin therapies, respectively. Twenty-four (16.1%) patients required oxygen support therapy by non-invasive ventilation or high-flow nasal cannula for 4–12 days (median 6 days [IQR 5–9]). Ten patients needed to switch between different oxygen support treatment modes. Eight patients required invasive mechanical ventilation for 3–14 days (median 9 [6–11]), three of whom were treated with extracorporeal membrane oxygenation (ECMO).

3.7 | Clinical outcomes of COVID-19 patients

As of March 6, 146 (98%) of patients were discharged, and 3 (2%) patients died (Table 4). The ages of the 3 patients who died were 79, 33 and 30 years, respectively. The 79-year-old female patient and the 33-year-old male patient had the comorbidities of coronary heart disease and fatty liver disease, respectively, and the 30-year-old

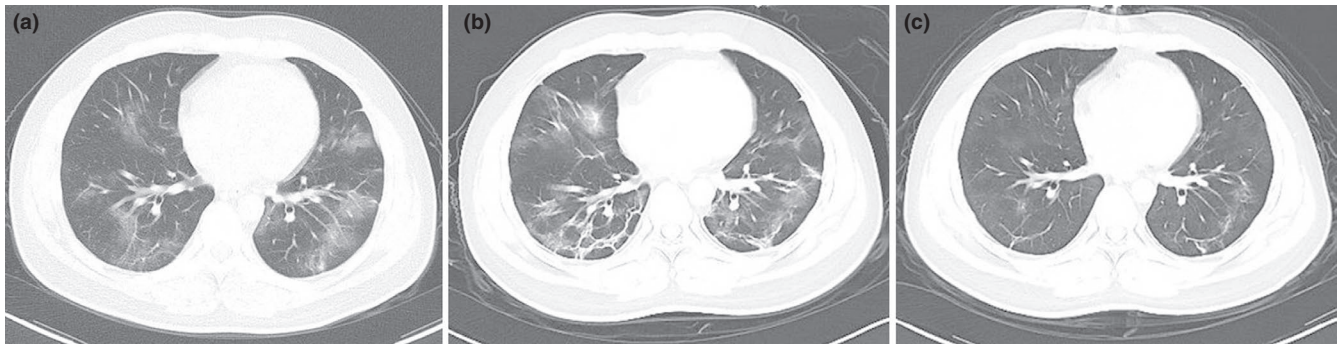


FIGURE 1 Dynamic changes in chest CT images of a patient with laboratory-confirmed COVID-19. (a) Chest CT images showing bilateral ground-glass opacity and patchy shadows in the patient with laboratory-confirmed COVID-19 on admission (testing of SARS-CoV-2 RNA positive for the first time on the same day). (b) The chest imaging showed significantly aggravated lung tissue, accompanied by vascular shadow and focal bronchiectasis, as well as pulmonary fibrosis, on the fourth day after admission. (c) Chest CT images showing bilateral ground-glass opacity and patchy shadows were improved and the inflammatory exudation was absorbed 13 days after admission; on the same day, his test for SARS-CoV-2 RNA was negative for the first time

woman was pregnant. The median SARS-CoV-2 shedding period and full clinical course were 12 (IQR: 9–17; mean: 13.4, 95% CI: 12.5, 14.2) and 20 (IQR: 16–24; mean: 21.2, 95% CI: 20.1, 22.3) days, respectively. The shortest and longest viral shedding durations were 5 and 35 days, respectively. The shortest and longest full clinical courses were 9 and 44 days, respectively.

3.8 | Viral shedding duration and full clinical course in different subgroups

The viral shedding duration and full clinical course in ICU patients were both significantly longer than those of non-ICU care patients (Table 5). Notably, SARS-CoV-2 RNA clearance occurred at least two days (2, 3 and 15 days, respectively) before death in the 3 patients who died. Additionally, compared with patients treated with supportive therapy, patients treated with any anti-viral agent or combination had a similar viral shedding duration and full clinical course (Table 6). Furthermore, compared with the supportive therapy group, no significant differences for the viral shedding duration and or full clinical course were observed after the division of the anti-viral treatment group into the detailed anti-viral agent(s) subgroups. Notably, we found that the SARS-CoV-2 RNA clearance was closely synchronized with or occurred earlier than the absorptions of lung inflammations (Figure 1) in the majority of patients, and a minority of patients had delayed absorptions of lung inflammations after SARS-CoV-2 RNA clearance.

4 | DISCUSSION

The current study is the first large-scale, multicentre, observational cohort to solely focus on the epidemiological and clinical characteristics, especially the viral shedding duration and full clinical course, of COVID-19 patients near Hubei Province in

China. The study included a total of 149 patients from 12 centres in Henan and Shaanxi Provinces. These two provinces are the neighbouring provinces of Hubei Province and were severely affected by SARS-CoV-2, especially Henan Province (WHO, 2020a). Notably, several important characteristics were observed, including a shorter viral shedding duration and clinical course than the Wuhan cohort (Zhou et al., 2020). Additionally, any current anti-viral agent or combination did not shorten the viral shedding duration or the clinical course in real-life settings, and SARS-CoV-2 RNA clearance occurred before fatality.

In the current study, 18.1% (27/149) of patients required care in the ICU within one week after hospital admission, and 3 patients died. We observed that ICU patients had older age (55 vs. 38 years); higher prevalence of dyspnoea (63% vs. 4.9%); and higher levels of procalcitonin, CRP, ESR, LDH and D-dimer on admission than non-ICU patients (Table 3). The mortality rate of Henan Province is lower than that of Hubei Province (WHO, 2020a), although Henan Province is the province closest to Wuhan City. The reduced mortality rate may be attributed to the epidemiological characteristics of these patients. In the current study, none of the patients (0%; 0/149) were exposed to the Huanan seafood wholesale market, which was presumed as the initial infection source, and 49% (73/149) were not exposed to Hubei Province, that is the majority of patients can be regarded as the second or even third generation or wave of patients. Additionally, these patients who had not been to Hubei Province may have been infected by exposure to their COVID-19 family members or other patients with COVID-19, suggesting the person-to-person transmission route as described previously (Chan et al., 2020; Li et al., 2020).

Notably, we found that the period of viral shedding of patients near Hubei Province was at least 12 (9–17) days (Table 4), that is from the first available positivity date to the first negativity date. Additionally, the median full clinical course for COVID-19 patients was 20 (16–24) days. However, the ICU patients had longer periods of viral shedding and clinical courses than the non-ICU patients (Table 5). The current results are different from those of a previous

TABLE 3 Selected differences between ICU and non-ICU COVID-19 patients on admission

	ICU care (n = 27)	Non-ICU care (n = 122)	p value
Age, years			
Mean (range)	55 (45–72)	38 (28–51)	<.0001
≥70	8 (29.6%)	5 (4.1%)	<.0001
<70	19 (70.4%)	117 (95.9%)	–
Leucocytes, × 10 ⁹ /L	6.6 (4.7–11.5)	4.7 (3.6–5.9)	<.0001
<3.5	3 (11.1%)	26 (21.3%)	–
3.5–9.5	15 (55.6%)	93 (76.2%)	–
>9.5	9 (33.3%)	3 (2.5%)	<.0001
Neutrophil count, × 10 ⁹ /L	5.6 (3.2–10.4)	2.9 (2.1–3.8)	<.0001
<1.8	1 (3.7%)	15 (12.3%)	–
1.8–6.3	15 (55.6%)	101 (82.8%)	–
>6.3	11 (40.7%)	6 (4.9%)	<.0001
Lymphocyte count, × 10 ⁹ /L	0.8 (0.4–1)	1.2 (0.8–1.5)	<.0001
<1.1	21 (77.8%)	55 (45.1%)	.002
1.1–3.2	6 (22.2%)	66 (54.1%)	–
>3.2	0 (0)	1 (0.8%)	–
Haemoglobin, g/L	131 (121–148)	140.5 (127–155)	.035
<130	13 (48.15%)	35 (28.7%)	.050
130–175	13 (48.15%)	87 (71.3%)	–
>175	1 (3.7%)	0 (0)	–
C-reactive protein, mg/L	62.4 (24.5–83.9)	12.7 (5.8–26.1)	<.0001
0–5	1 (3.7%)	30 (24.6%)	–
>5	26 (96.3%)	92 (75.4%)	.016
Erythrocyte sedimentation rate, mm/h	44 (30–58.5)	20 (11–37.7)	<.0001
0–15	0/22 (0)	41/115(35.7%)	–
>15	22/22 (100%)	74/115 (64.3%)	<.0001
Procalcitonin, ng/mL	0.16 (0.09–0.38)	0.041 (0.02–0.08)	<.0001
0–0.046	1 (3.7%)	64/116 (55.2%)	–
>0.046	26 (96.3%)	52/116 (44.8%)	<.0001
Alanine aminotransferase, U/L	30 (21–57)	20 (14–28.8)	<.0001
0–40	18 (66.7%)	110/120 (91.7%)	–
>40	9 (33.3%)	10/120 (8.3%)	<.0001
Aspartate aminotransferase, U/L	38 (30–60)	23 (19–33)	<.0001
0–40	15 (55.6%)	110/120 (91.7%)	–
>40	12 (44.4%)	10/120 (8.3%)	<.0001
Gamma-glutamyltransferase, U/L	38 (22–58)	29 (20–40)	.035
0–58	20 (74.1%)	111/120 (92.5%)	–
>58	7 (25.9%)	9/120 (7.5%)	.005
Albumin, g/L	33 (30.1–40.3)	42 (39–45)	<.0001
<35	14 (51.9%)	10/120 (8.3%)	<.0001
35–55	13 (48.1%)	108/120 (90%)	–
>55	0 (0)	2 (1.7%)	–
Lactate dehydrogenase, U/L	404 (273–496)	200 (150.8–230)	<.0001
<75	0 (0)	2/120 (1.7%)	–
75–245	3 (11.1%)	95/120 (79.1%)	–

(Continues)

TABLE 3 (Continued)

	ICU care (n = 27)	Non-ICU care (n = 122)	p value
>245	24 (88.9%)	23/120 (19.2%)	<.0001
Serum sodium, mmol/L	135 (133–140)	140 (137.1–142)	<.0001
<135	11 (40.7%)	8/120 (6.7%)	<.0001
135–153	16 (59.3%)	112/120 (93.3%)	–
D-dimer, mg/L	0.55 (0.22–4.6)	0.3 (0.21–0.5)	.034
0–0.55	14 (51.9%)	94/120 (78.3%)	–
>0.55	13 (48.1%)	26/120 (21.7%)	.005
Dyspnoea	17 (63%)	6 (4.9%)	<.0001
Respiratory rate > 24 breaths per minute	20 (74.1%)	16 (13.1%)	<.0001

Note: Data are presented as the median (IQR), n (%) or n/N (%), where N is the total number of patients with available data.

Abbreviations: COVID-19, coronavirus diseases 2019; ICU, intensive care unit.

report in the Wuhan cohort, which indicated that the median duration of viral shedding was 20 days (IQR 17–24) in survivors (Zhou et al., 2020). The most likely explanation is that the patients from the Wuhan cohort had more severe cases. However, it is important to note that the actual period of viral shedding may be longer than the current finding because the viral positivity time point may be as early as the incubation period or before their first visits or admissions to hospitals.

Additionally, SARS-CoV-2 RNA clearance developed at least 2 days before death in all 3 patients who died in the current study. This phenomenon is also different from the previous study (Zhou et al., 2020), which indicated that SARS-CoV-2 was detectable until death in non-survivors. The cause of this difference is unknown. It is important to note that fatalities in the current study were caused by the gradually developed fatal complications beyond the pneumonia itself. Furthermore, all 3 patients who died had the specific conditions, that is the coronary heart disease, fatty liver diseases and pregnancy, which may be the precipitating factors. Notably, only one was an older person, and the other 2 patients were only 33 and 30 years. This finding indicates that young COVID-19 patients also have a risk of fatality when they have some comorbidities or specific conditions.

Notably, we found that the viral shedding duration and full clinical course were similar in the anti-viral treatment subgroup and the support therapy group (Table 6). The anti-viral agents included oseltamivir, lopinavir/ritonavir, arbidol, peramivir, interferon α and any combinations thereof. This result is consistent with the conclusion of the recent study by Cao et al. (2020), that is no benefit was observed with lopinavir/ritonavir treatment beyond standard care, which is similar to the supportive therapy in the current study. Therefore, future effective anti-viral treatment studies are urgently needed.

SARS-CoV-2 leads to pneumonia and has various signs and symptoms, such as fever, cough, fatigue or even dyspnoea (Carlos, Dela Cruz, Cao, Pasnick, & Jamil, 2020; Chen et al., 2020; Chung et al., 2020; Del Rio & Malani, 2020; Wang, Hu, et al., 2020). The current study has similar findings. Notably, we found that 10.7%

(16/149) of laboratory-confirmed cases did not have fever, and eight patients did not have any signs or symptoms. Furthermore, 9% (13/144) of patients with available chest CT data did not have pneumonia presentations on chest CT scans. These patients with laboratory-confirmed SARS-CoV-2 infection with or without pneumonia and asymptomatic patients were diagnosed only because their family members had laboratory-confirmed cases, and they were then tested. These asymptomatic SARS-CoV-2-infected populations may be the important infection sources (Bai et al., 2020), and the prompt detection and proper management of these patients are meaningful for the control of SARS-CoV-2 transmission.

A previous study indicated that 43.4% (43/99) of patients had various degrees of liver injury, which was demonstrated by elevations of ALT or AST (Chen et al., 2020). In the current study, we found that 19% (28/147) of patients had increased ALT or AST levels in the laboratory-confirmed group. Eight patients had an explicit history of chronic liver diseases. Additionally, it is important to note that the majority of patients had a drug-taken history before admission, mainly including acetaminophen and traditional Chinese medicines. These drugs may also cause liver injury. Therefore, the causality of SARS-CoV-2 and liver injury is largely unknown and needs further investigation.

The other feature of the current study is that this cohort covers all age groups of COVID-19 patients. Notably, we found that eight children patients aged two to ten years old had mild signs or symptoms. Three children did not have fever, and the other three children had the sole symptom of diarrhoea. In contrast, among the older patients, 8 (29.6%) and 5 (4.1%) patients were aged more than 70 years in the ICU and non-ICU groups, respectively (p value <.001, Table 3). For the sex susceptibility, we indeed found a greater number of males (91/149, 61.1%) than females (58/149, 38.9%) in 149 patients. This result is similar to what was found for the previous SARS-CoV (Channappanavar et al., 2017) and Middle East respiratory syndrome (MERS)-CoV (Badawi & Ryoo, 2016) and to current SARS-CoV-2 studies (Chen et al., 2020; Guan et al., 2020; Huang et al., 2020). However, some other studies did not present explicit differences in sex susceptibility (Li et al., 2020; Wang, Hu,

TABLE 4 Treatments and outcomes of COVID-19 patients

	COVID-19 patients (n = 149)
Treatment	
Any therapy	138 (92.6%)
Anti-viral treatment	80/138 (58%)
Oseltamivir	17/138 (12.3%)
Interferon α (aerosol inhalation, the same below)	11/138 (8%)
Lopinavir/Ritonavir	7/138 (5.1%)
Arbidol	6/138 (4.3%)
Peramivir	1/138 (0.7%)
Oseltamivir, Lopinavir/Ritonavir	20/138 (14.5%)
Lopinavir/Ritonavir, Interferon α	12/138 (8.7%)
Peramivir, Lopinavir/Ritonavir	6/138 (4.4%)
Glucocorticoids	25 (16.8%)
Intravenous immunoglobulin therapy	26 (17.4%)
Traditional Chinese medicine	34 (19%)
Oxygen support therapy	55 (36.9%)
Nasal cannula	34 (22.8%)
Non-invasive ventilation or high-flow nasal cannula	24 (16.1%)
Invasive mechanical ventilation	8 (5.4%)
Invasive mechanical ventilation and ECMO	3 (2%)
Switch between different oxygen support modes	9 (6%)
Continuous renal replacement therapy	0 (0)
Complications during hospitalization	
Acute liver injury	5 (3.4%)
Secondary infection	5 (3.4%)
Acute diarrhoea	4 (2.7%)
Acute respiratory distress syndrome	4 (2.7%)
Septic shock	3 (2%)
Acute renal injury	1 (0.7%)
Premature delivery	2/3 (66.7%)
Clinical outcome	
Remained in hospital	0 (0)
Discharge	146 (98%)
Fatality	3 (2%)
SARS-CoV-2 shedding period, days	12 (9–17)
Full clinical course, days	20 (16–24)

Note: Data are presented as the median (IQR), n (%) or n/N (%), where N is the total number of patients with available data.

Abbreviations: COVID-19, coronavirus diseases 2019; ECMO, extracorporeal membrane oxygenation; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

et al., 2020). It is important to note that the mobility for males is greater than that for females in China, especially for rural regions, and the male agricultural workers are always going outside for work,

while females are always staying at home to take care of the family. Male mobility may increase the infection risk. Therefore, we suspected that the female sex itself may not play a protective role and that individuals may be widely susceptible to SARS-CoV-2 infection regardless of sex.

Additionally, we presented data from additional three pregnant women. Two women in the late stage of pregnancy required premature delivery, and one newborn had pneumonia and required care in the ICU. Fortunately, the SARS-CoV-2 RNA results of the two newborns were all negative. It is largely unknown whether SARS-CoV-2 infection can contribute to premature delivery or intra-uterine vertical transmission, and future studies are needed. The preliminary conclusion of the current study suggested that SARS-CoV-2 infection may be associated with premature delivery, but no evidence of mother-to-child transmission was found.

Our study has several limitations. First, only 149 patients were included in this multicentre, retrospective study in Henan and Shaanxi Provinces, and the findings may only indicate the characteristics of only these two provinces. Second, no recognized effective treatment has been given to patients, which may lead to the administration of various treatment regimens according to the previous SARS-CoV and MERS-CoV reports (Arabi et al., 2018; Chu et al., 2004; Falzarano et al., 2013; Groneberg et al., 2005; Sheahan et al., 2020), or even empirical therapy for patients, and, eventually, these anti-viral treatments proved ineffective in the current study. Furthermore, potential sources of bias may exist in this study. However, it is known that Henan Province had the third largest number of SARS-CoV-2-infected patients in China (WHO, 2020a), and the majority of patients came from Xinyang, Zhengzhou and Nanyang cities of Henan Province. In the current study, the vast majority of patients were from the largest designated local hospitals of the above three cities, which may avoid the potential sources of bias to the largest extent.

In conclusion, to the best of our knowledge, we present the first data on the viral shedding period and complete clinical course of COVID-19 in a large cohort near Hubei Province, and these parameters were shorter than those in previous reports from cohorts in Wuhan City of Hubei Province. Additionally, SARS-CoV-2 clearance can occur at least two days before death, at least in three non-survivors of the current study. Furthermore, we first indicate that current anti-viral treatments did not present the benefit of shortening the viral shedding period or the clinical course in real-world settings. These findings expand our knowledge of SARS-CoV-2 infection and may be helpful for the management of the epidemic outbreak of COVID-19 worldwide. Further studies concerning effective anti-viral agents and vaccines are urgently needed.

ETHICS APPROVAL

The study protocol was approved by the Institutional Review Commission of The First Affiliated Hospital of Zhengzhou University, and the requirement for informed consent was waived

TABLE 5 SARS-CoV-2 shedding period and full clinical course of ICU, non-ICU and fatality groups

	ICU (n = 27)	Non-ICU (n = 122)	Fatality (n = 3)	Survivors (n = 146)	p value*
Viral shedding period, days	21 (17–24)	11 (9–15)	13 (7, 24)	12 (9–17)	<.0001
Clinical course, days	30 (22–33)	19 (15.8–22)	20 (16, 43)	20 (16–26)	<.0001

Note: Data are presented as the median (IQR). *Comparisons between ICU and non-ICU groups. Abbreviations: ICU, intensive care unit; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

TABLE 6 SARS-CoV-2 shedding period and full clinical course of anti-viral-treated and anti-viral-untreated groups

	Anti-viral treatment group (n = 80)	Supportive therapy group (n = 58)	p Value
SARS-CoV-2 shedding period, days	12.5 (10–17)	12 (9–17)	.447
Full clinical course, days	21 (17–24.8)	18.5 (15–24.3)	.250

Note: Data are presented as the median (IQR). Patients treated with any anti-viral agent or a combination of anti-viral agents were included in the anti-viral treatment group, and the anti-viral agents included oseltamivir, lopinavir/ritonavir, arbidol, peramivir and interferon α (aerosol inhalation). Patients not treated any anti-viral agent or a combination of anti-viral agents were included in the supportive therapy group, and the detailed treatment regimens included glucocorticoids, intravenous immunoglobulin therapy, traditional Chinese medicine, oxygen support therapy and symptomatic therapy. Additionally, compared with the supportive therapy group, no significant differences for the viral shedding duration or full clinical course were observed after division of the anti-viral treatment group into the detailed anti-viral agent(s) subgroups. Abbreviation: SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

by the Institutional Review Commission in light of de-identified data of patients and the urgent need to collect data.

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CONFLICT OF INTEREST

The authors declare that they have no competing interests.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analysed in this study. All available data (results) are presented in this article.

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